

REMARKS

Status of the Application

All claims pending in the application stand rejected. Claims 1, 8-10, 13-15 and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Palmieri *et al.*, S.T.P. Pharma Sciences pages 188-194 (1996) (“Palmieri *et al.*”), and U.S. Patent 5,545,628 (“‘628”). Claims 1, 8-10, 13-15 and 22 are rejected under the non statutory double patenting rejection in view of U.S. Patent 6,465,011 (“‘011”)

Amendments

Claims 1, 8-10, 13-15 and 22 are cancelled. New claims 24 to 32 are added. New claims 24 to 32 more clearly describe the preferred embodiment of the solid dispersion composition of the present invention, indicating that the fenofibrate is in the amorphous state and said amorphous fenofibrate is dispersed into a PEG matrix, to which HPMC is further added to inhibit the amorphous fenofibrate to become crystallized fenofibrate. Applicants submit that there is no new subject matter added as a consequence of the new set of claims; support will be indicated in the discussion of the rejections.

Rejection under 35 U.S.C. § 103

Claims 1, 13-15, 18 and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Palmieri *et al.*, and ‘628.

The Examiner sustains that “*it would have been obvious to one of ordinary skill in the art to prepare fenofibrate composition taught by Palmieri et al., article using ethanol as solvent and PEG as the carrier and adding HPMC so that solid dispersions are formed. One of ordinary skill in the art would be motivated to add HPMC in fenofibrate dispersions of Palmieri et al with the reasonable expectation of success that HPMC avoids the formation of Fenofibrate crystals. This is a prima facie case of obviousness.*” (page 3 of Office Action).

The Examiner responds to Applicants’ arguments by stating: “*Palmieri et al. article teaches Fenofibrate dispersions except the claimed HPMC and patent ‘628 teaches Fenofibrate compositions and at col. 2 teaches to one skilled in the art that certain compounds are added to prevent crystal formation...*” (page 4 of Office Action).

Applicants respectfully disagree with the Examiner's comments. Applicants submit that there are pivotal differences between the dispersion described in Palmieri *et al.*, the dispersion described in '628, and the dispersion in the present application.

Palmieri *et al.* describes that a solid dispersion of crystalline fenofibrate could be prepared in PEG 4000, and that fenofibrate solubility is substantially increased by an increased carrier/drug ratio and a low percentage of fenofibrate in the total amount of solid components. Palmieri *et al.* does not mention the use of HPMC to improve the solubility of said fenofibrate solid dispersion.

'628 discloses a liquid formulation of fenofibrate, which is a totally different composition than a solid dispersion as the one described either by Palmieri *et al.*, or by the description of the present application. The Office Action refers to col. 2, lines 44-54, of '628. That paragraph indicates that the suspension stabilizer (which includes HPMC) avoids the formation of fenofibrate crystals, i.e. avoids that the liquid fenofibrate changes into fenofibrate crystals (see col. 2, lines 46-54). That '628 teaches a fenofibrate solution is also indicated in other paragraphs, i.e. col. 2, lines 56-59; col. 3, lines 39-44; col. 4 lines 1-10.

Applicants submit that a person skilled in the art did not need to add HPMC to the composition described in Palmieri *et al.* because the composition described in Palmieri *et al.* is not a liquid formulation, and the fenofibrate is in a crystalline solid state.

It is very important to observe that the general language "inhibition or prevention of crystallization" has a different meaning in '628 compared to the meaning given in the present application. In '628 the purpose of suspension stabilizers (HPMC) is to avoid that the liquid state of fenofibrate forms a crystalline solid state. In the present application the meaning of adding HPMC is to avoid that the solid amorphous state of fenofibrate changes into a crystalline state. These are two totally different physical processes. Claim 1 has been changed to indicate that it is amorphous fenofibrate what is dispersed in PEG and that the addition of HPMC is to prevent the amorphous state to change into a crystal state. There is ample support in the description for this process occurring with fenofibrate. See for instance, Example 1, part E, explaining the results for fenofibrate (page 24). Amorphous fenofibrate dispersed in PEG begins to crystallize within one hour (Figure 10), after adding PVP (similar amorphous polymer as HPMC) to

the fenofibrate-PEG dispersion, the fenofibrate does not crystallize in the timeframe of the experiment (Figure 11).

Therefore, Applicants submit that it is not obvious to use HPMC with the purpose of avoiding crystallization of amorphous fenofibrate in a composition, after reading a disclosure that describes the potential use of HPMC with the purpose of maintaining the liquid state of fenofibrate.

Accordingly, in view of new claim 1 and the foregoing arguments, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) obviousness rejection.

Double patenting

Claims 1, 8-10 and 22 are rejected on the ground of non statutory obviousness-type double patenting over claims 1-3 and 5-9 of U.S. patent 6,465,011 (“’011”) in view of Palmieri *et al.* article. Applicants submit that the Examiner is using impermissible hindsight to reach to the conclusion that “*it would have been obvious to prepare compositions of ’011 claimed in the patent and add PEG with reasonable expectation of success that increased dissolution and increased bioavailability of fenofibrate dispersions is obtained*” (page 6 of the Office Action).

Palmieri *et al.*, describes that a solid dispersion of crystalline fenofibrate could be prepared in PEG 4000, and that fenofibrate solubility can be substantially increased by keeping fenofibrate below 15% on the powder and by an increased carrier/drug ratio. Palmieri *et al.* does not mention the use of HPMC to improve the solubility of said fenofibrate solid dispersion.

’011 describes a solid amorphous solid state of fenofibrate dispersed in HPMC, PVP, or Eudragit®. The amorphous polymer carries the fenofibrate in amorphous state.

The present application discloses and claims a solid dispersion of amorphous fenofibrate dispersed in PEG, which further comprises HPMC. There are no indications that a skilled in the art would have tried to use HPMC in a preparation such as that described in Palmieri *et al.* wherein Palmieri *et al.* exclusively describes that by increasing the PEG:fenofibrate ratio to 90:10, and by keeping fenofibrate in the powder

lower than 15%, the dissolution and bioavailability characteristics of fenofibrate are improved

It is important to understand that the present application does not claim adding PEG to the composition claimed in '011 in order to increase dissolution and bioavailability of fenofibrate dispersions, as the Examiner seems to suggest. On the contrary, the present application is a solid dispersion of fenofibrate in PEG, to which HPMC is added to inhibit the amorphous form of fenofibrate to become crystallized, with the benefit of a better dissolution pattern of fenofibrate.

CONCLUSION

In view of the new set of claims and the aforementioned remarks, Applicants respectfully request the Examiner to reconsider the application and withdraw all outstanding rejections. Applicants submit that the application is now in condition for allowance, which action is earnestly solicited.

Should the Examiner have any concerns regarding the above, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR §1.16, as well as any patent application processing fees under 37 CFR §1.17 associated with this communication for which full payment had not been tendered, to Deposit Account No. 01-0025. Any deficiency or overpayment should be charged or credited to the above-numbered deposit account.

Respectfully submitted,
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